have Applicants amended claim 1 prior to the present response. The Examiner is asked to clarify his statement.

Applicants have cancelled claims 78, 112, 124, 135, 136, 142, 150 and 152 as drawn to non-elected inventions.

Applicants respectfully request that the Examiner clarify whether Groups I and II have been rejoined because claim 55 appears to be pending (see Office Action Summary, page 1) even though it was originally in Group II, and thus was considered a non-elected claim. If claim 55 has not been rejoined to the currently pending claims, Applicants respectfully request that it be cancelled.

Claims 1, 31 and 100 have now been amended to include the size limitation of at least six nucleotides. Support for the amendment can be found in the specification on page 18, lines 25-28.

Claims 1, 31 and 100 have been further amended to include the limitation the immunostimulatory nucleic acid has a phosphorothioate backbone linkage. Support can be found in the specification on page 19, lines 5-9.

No new matter has been added.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 1-31, 52 and 100 are rejected under 35 U.S.C. §112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicants have amended claims 1, 31 and 100, and herewith respectfully traverse the rejection in view of these amendments and the arguments provided below.

The claimed invention relates to methods of administering to a subject an antigen and a Th2 immunostimulatory nucleic acid, at least six nucleotides in length and having a phosphorothioate backbone linkage, to induce an antigen-specific immune response. The Th2 immunostimulatory nucleic acid as defined in the specification on page 26, lines 9-15 lacks a CpG dinucleotide and it additionally is not T-rich or does not contain a poly T motif (i.e., a TTTT motif), a poly G motif (i.e., a GGGG motif), or a methylated CpG motif. The Th2 immunostimulatory nucleic acid induces an immune response that is predominately Th2 in nature (i.e., an immune response that involves the induction of at least one Th2 cytokine or antibody typical of a Th2 response). The nucleic acid may be administered mucosally, dermally

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or parenterally, although higher doses of nucleic acid are required for this latter route of administration. The Examples provided demonstrate the induction of antigen-specific Th2 immune responses upon administration of nucleic acids orally and with an antigen in a murine model.

The Examiner states that the breadth of the claims is not enabled. Whether a claimed invention is enabled rests on whether undue experimentation would be required for one of ordinary skill in the art to practice the invention. Undue experimentation reflects the quality rather than the quantity of experimentation needed. Whether experimentation is undue is determined by an analysis of the factors set forth in *In re Wands*. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality. Rather, it appears that only some of these factors (e.g., breadth of the claims, the state of the prior art at the time of filing, and the working examples) were considered by the Examiner. Consideration of the *Wands* factors as a whole leads one of ordinary skill to the reasonable conclusion that practicing the claimed invention would not require undue experimentation.

With respect to the breadth of the claims, the Examiner stated that the specification, "while being enabling for method of employing Th2 immunostimulatory nucleic acid of at least 8 nucleotides and comprising 5' TCCA 3' as a Th2 adjuvant in combination with an antigen for mucosal administration to a vertebrate, does not reasonably provide enablement for any other claimed embodiment." The claims as pending relate to the administration of an antigen and a Th2 immunostimulatory nucleic acid, that is at least 6 nucleotides in length and that has a phosphorothioate backbone linkage, to a subject either by mucosal, dermal or parenteral routes, in order to induce an antigen-specific immune response. Applicants respectfully maintain that the scope of the pending claims parallels the working examples provided, and is consistent with the state of the art at the time of filing.

The Examiner cites several references as being representative of the state of the prior art. The Examiner then states that "the issue is then whether or not a skilled artisan on the basis of the applicant's disclosure would have reasonably be able to extrapolate the rather unexpected results as demonstrated by the as-filed specification to the full breadth of the claims." Applicants respectfully traverse this statement as the prior art is not to be used to "extrapolate" the claimed invention. In fact, the novelty and non-obvious requirements of the patent law preclude such extrapolation.

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In addition, the art cited by the Examiner does not evidence the state of the art at the time of filing. The instant application was filed on January 22, 2001, with a priority date of January 20, 2000. Several of the references cited by the Examiner date back as far as 1993, seven years before the earliest priority date of the instant application.

The Examiner cites Yamamoto et al. (1994) and describes it as teaching that "the use of a specific palindromic sequence and some molecular size of synthetic nucleic acid DNA is required to induce that biological activity." Yamamoto et al. studied the ability of nucleic acids containing a specific palindrome to induce IFN production and augment NK activity for splenocytes. Respectfully, Yamamoto et al. were tracking aspects of a Th1 immune response, a biological activity different from that of the present invention. Thus, the relevance of Yamamoto et al. is unclear. The state of the art at the time of filing included the realization that certain nucleic acids could induce a Th1 immune response when administered in vivo, absent any anti-sense effects. The Examples of the instant specification clearly demonstrate the identification of immunostimulatory nucleic acids capable of inducing an antigen-specific Th2 immune response upon mucosal administration with an antigen to a murine subject. These nucleic acids need not possess a palindrome in order to effect their particular biological activity.

The Examiner also cites Messina et al. (1993) and characterizes it as teaching that the "mechanism by which DNA triggers proliferation is not known." The Examiner is respectfully reminded that patentability does not rest on an understanding of mechanism. Notwithstanding this, however, the teaching of Messina et al. reflects the state of the art seven years prior to the filing date. Since the Messina et al. reference the mechanism of nucleic acid immunostimulation has been further elucidated including the identification of particular motifs (e.g., poly T motifs) and the involvement of particular receptors (e.g., the Toll-like receptors that bind CpG nucleic acids) in Th1 immune response induction.

The Examiner also cites Branda et al. (1996) and states that it teaches that "inspection of the oligodeoxynucleotides known to enhance B cell function...fails to show any important homologies". Applicants question the relevance of the Branda et al. reference given that the experiments reported by Branda et al. focus on B cell activation and measurement of total IgG production. Branda et al. did not analyze Th2 IgG isotypes specifically and thus these findings are not relevant to the claimed invention. Moreover, Branda et al. report that some but not all CpG nucleic acids are capable of stimulating B cells. Applicants reiterate that the nucleic acids

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of the claimed invention do not possess a CpG motif. The teachings of Yamamoto et al., Messina et al. and Branda et al. do not negate the enabling nature of the specification, at least because they relate to different nucleic acid species, to different biological outcomes, and most importantly do not reflect the state of the art at the time of filing.

The Examiner further cites the instant specification and McCluskie et al. (2001) for the teaching that "the stimulatory effects of non-CpG ODN ... were totally unexpected since non-CpG ODN do not have such an effect when delivered by a parenteral route (e.g., IM injection)". The instant specification on page 3, lines 24-26 teaches that "the effective amount (of a Th2 immunostimulatory nucleic acid) is generally much lower (when administered mucosally or dermally) than that required to induce an immune response when administered parenterally." This teaching is found throughout the specification, and it simply reflects the need for a larger dose of nucleic acid if administration is parenteral versus mucosal or dermal. It does not negate the enabling nature of the specification.

The state of the art at the time of filing included a knowledge of various aspects of Th1 immunostimulatory nucleic acids including information about the ability of certain nucleic acids to stimulate both innate and antigen-specific immune responses and the successful administration of such nucleic acids for therapeutic effect, including adjuvant effect. The state of the art also included an understanding of the distinction between Th1 and Th2 immune responses including their different effects, and their involvement in normal immune development and maturation and in abnormal disease states.

With regard to the working examples, the Examiner contends that the inability to correlate the murine results of the Examples with therapeutic methods in humans, and the lack of alternative animal models, renders the Examples insufficient for purposes of enablement. The Examiner cites McCluskie et al. (1999) as teaching that DNA vaccine results in mice are not generally predictive of results in humans. The McCluskie et al. reference taken as a whole is not teaching that animal models are not useful in developing human therapeutics. Rather, the McCluskie et al. reference relates to the administration and therapeutic effects of DNA vaccines, which by definition must induce their effects via expression of encoded proteins. Applicants submit that the nucleic acids of the instant invention need not encode a therapeutic protein in order to be immunostimulatory.

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Also, even if as the Examiner asserts McCluskie et al. teaches that "the generally absent responses with the noninjected routes were not unexpected, as the mucosal surfaces are protective barriers, physiologically designed to limit uptake of bacteria, viruses, and antigens", this would still not preclude their efficacy as Applicants have demonstrated in the Examples that the non-CpG nucleic acids are immunostimulatory when administered via an oral route. The section of the McCluskie et al. publication referred to by the Examiner includes a discussion of nucleic acid administration routes and the possibility of degradation in routes such as mucosal administration. Applicants submit that the risk of degradation may be an obstacle to DNA vaccine technology, which generally requires that administered nucleic acids remain intact in order to express full length therapeutic proteins. However, this is a significant difference with the methods of the pending claims, which do not require protein expression from the administered nucleic acid. The nucleic acids of the claimed methods can be effective even at short lengths (e.g., 6 nucleotides or greater). As a result, the teachings of McCluskie et al. are generally not relevant to the pending claims, at least because the pending claims do not require expression and/or subsequent delivery of a therapeutic protein encoded by an administered nucleic acid.

McCluskie et al. may be read to teach that higher doses of nucleic acids may be required to stimulate an immune response in a human subject as compared to the doses that are required in a murine subject. The working examples however clearly demonstrate induction of an immune response using non-CpG containing nucleic acids in an *in vivo* murine model. The Examples are therefore predictive that non-CpG containing nucleic acids will behave similarly in humans, even if higher doses are required. Testing to determine the amount of nucleic acid to deliver to human subject is within the mandate of the FDA, not the Patent Office. Patentability does not rest on the showing of efficacy in a human subject.

Where the working examples correlate with the scope of the pending claims, such examples are to be given weight in the Wands analysis. Applicants submit that a strong correlation exists between the working examples and the claimed methods. The working examples demonstrate that administration of an immunostimulatory nucleic acids with six or more nucleotides lacking a CpG dinucleotide induce an antigen-specific immune response in an *in vivo* murine model when administered together with an antigen. The claimed methods require administration of the same class of nucleic acids in a variety of species for the same purpose.

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Applicants respectfully assert that the Examples clearly parallel the scope of the claimed methods.

An enablement analysis should also include evaluation of the remaining *Wands* factors. These factors include: 1) guidance presented, 2) nature of the invention, 3) relative skill of those in the art, 4) predictability of the art, and 5) the quantity of experimentation required. Respectfully, Applicants submit that the evaluation of these remaining factors supports the conclusion that the invention is indeed enabled.

Applicants assert that the specification provides extensive guidance as to the identification and use of Th2 immunostimulatory nucleic acids in the claimed methods. The specification teaches how to select and test putative nucleic acids, the subjects to be treated using the nucleic acids, their routes of administration, and the like. Thus the guidance presented is sufficient.

The nature of the invention is the use of nucleic acids to induce an antigen-specific Th2 immune response in a subject when administered with an antigen. Adjuvants are known in the art, as are antigen-specific immune responses.

Applicants contend that the level of skill in the art relevant to the invention at the time of filing was high. The level of skill in the art has an important effect on the amount of guidance which must be provided to enable the invention. As the court stated in *In re Howarth*, "[i]n exchange for the patent, [the applicant] must enable others to practice his invention. An inventor need not, however, explain every detail since he is speaking to those skilled in the art." *In re Howarth*, 654 F.2d 103, 105 (CCPA 1981). Although the instant invention differs from the prior art Th1 nucleic acids, the established methods of making and administering the Th1 immunostimulatory nucleic acids would be applicable to making and using the Th2 immunostimulatory nucleic acids of the claimed invention. One of ordinary skill in the art would possess a level of understanding of how to make and use functional nucleic acids with immunostimulatory properties and would therefore, without undue experimentation, be able to apply the teachings provided in the instant application to the practice of the claimed invention.

The art of nucleic acid immune stimulation is also predictable, for at least the reasons provided above. The art is familiar with the ability of Th1 immunostimulatory nucleic acids to be immunostimulatory, and more particularly to act as adjuvants, in vivo. In addition, the art is familiar with Th2 immune responses.

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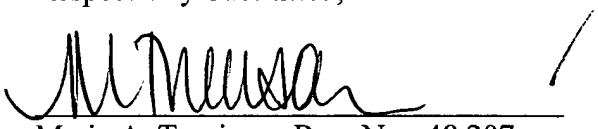
In summary, a full analysis of the *Wands* factors compels the conclusion that only routine, and not undue, experimentation is necessary to practice the claimed invention.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Summary

It is believed that all of the pending claims are in condition for allowance. If the Examiner has any questions or comments, he is encouraged to contact Applicants' representative at the number listed below.

Respectfully Submitted,



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Docket No.: C01040.70010.US
Date: February 18, 2003
X02.15.03

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APPENDIX A

Marked-up Claims

Please amend the claims as follows:

1. (Amended) A method for inducing an antigen specific immune response comprising: administering to a subject an antigen and a Th2-immunostimulatory nucleic acid, at least six nucleotides in length and having a phosphorothioate backbone linkage, in an amount effective to produce an antigen specific immune response when the Th2-immunostimulatory nucleic acid is administered mucosally or dermally.

31. (Amended) A method for inducing an antigen specific immune response comprising: administering to a subject an antigen and a Th2-immunostimulatory nucleic acid, at least six nucleotides in length and having a phosphorothioate backbone linkage, in an amount effective to produce an antigen specific immune response when the Th2-immunostimulatory nucleic acid is administered parenterally.

100. (Amended) A pharmaceutical composition, comprising:
an effective amount of a Th2 immunostimulatory nucleic acid, at least six nucleotides in length and having a phosphorothioate backbone linkage, for stimulating a Th2 immune response when administered mucosally or dermally, an antigen, and a pharmaceutically acceptable carrier.

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